REMARKS

Reconsideration of the present application is respectfully requested. The application includes claims 24-29, 31-37, 39-41, 44 and 46-66, pending and under consideration.

In the outstanding Office Action, claims 24-29, 31-37, 39-41, 44 and 46-66 are rejected under 35 U.S.C. §103(a) as being unpatentable over "the combined teachings of Bellini et al. in view of the acknowledged prior art and Martindale The Extra Pharmacopoeia." In traversal of this rejection, Applicant respectfully submits that the cited references, alone or in combination, do not teach or suggest the invention of the present claims or the desirability of the claimed invention.

In support of the rejection of the above-identified claims, the Examiner states that:

> Bellini et al. clearly disclose concentrated and diluted peritoneal dialysis solutions that contain electrolytes, gluconate salts such as iron gluconate and glucose and the ordinary skilled artisan has been taught that iron dextran can be administered intraperitoneally. The ordinary skilled artisan in this field is a highly educated and trained medical professional responsible for critical care of dialysis patients, who would not blindly formulate dialysis solution ingredients to induce a toxic reaction. Upon having been taught that iron gluconate and iron dextran may be given to dialysis patients by the intraperitoneal route, it would have been through routine experimentation that he/she would have arrived at the appropriate concentrations of electrolytes and iron gluconate or iron dextran (with a molecular weight of less than 50,000) suitable for a dialysis patient in need of iron supplementation as claimed.

(Office Action, Page 3). Applicant respectfully traverses this rejection and disagrees with the Examiner's interpretation of the teaching of Bellini et al. and the significance placed by the Examiner upon asserted prior art teaching of iron dextran in a peritoneal dialysate. Applicant's traversal is supported by the following facts, evidence of which is provided by the attached DECLARATION UNDER 37 C.F.R. §1.132 (hereafter "Declaration"): (1) iron dextran is not an iron complex as recited in the pending claims and as defined in the specification, and information

regarding the inclusion of iron dextran in a dialysate would not motivate a skilled artisan to include in a dialysate an iron complex as recited in the pending claims; and (2) in view of the context within which Bellini et al. must be considered, this reference does not teach or suggest, and would not motivate a skilled artisan to make or use, a dialysate composition including iron gluconate. In view of evidence now of record establishing these facts, Applicant submits that the cited prior art would not motivate a person of ordinary skill in the art to practice the present invention and that the claims are in condition for allowance.

In support of the present rejection, the Examiner asserts that "the ordinary skilled artisan has been taught that iron dextran can be administered intraperitoneally." In reply, it is important to recognize that the iron dextran compositions to which the Examiner refers do not fall within the scope of the pending claims. Each of the pending claims includes a recitation of "an iron complex dissolved in the water, the complex ... having a molecular weight of less than about 50,000." In contrast, iron dextran compositions identified by the Examiner are suspensions of macromolecules that include multiple dextran molecules and iron tightly bound in the form of macromolecules that have molecular weights of about 350,000. (Declaration, paragraph 4). Applicant would also draw the Examiner's attention to the paragraph spanning pages 21 and 22 of the present application, wherein such macromolecules are referred to as "secondary complexes" and are clearly distinguished from the presently claimed invention.

The specification of the present application and the attached Declaration both explain why macromolecules such as iron dextran have been historically selected for use as a vehicle for intramuscular and intravascular iron delivery. Namely, because iron dextran preparations are tightly formed, non-soluble macromolecules in aqueous suspension, and thus do not release free iron into the blood, medical providers in this field have considered them to be the only safe

vehicles for parenteral iron delivery. (Declaration, paragraph 5). Indeed, great efforts have been consistently made in the prior art to ensure that soluble iron was not contacted with blood due to the widespread belief that free iron is toxic. As stated at page 7 of the present application, "it is widely believed that soluble iron complexes are unacceptable iron delivery agents, this belief being based upon a fear of the toxicity of free iron in blood." (Specification, page 7, lines 5-8). This widespread belief is described in the specification and reiterated throughout the record of this case. It is also shown in recent publications, such as, for example, the attached paper by Gupta et al. (Gupta, A., Crumbliss, A., Treatment of iron deficiency anemia: are monomeric iron compounds suitable for parenteral administration? J Lab Clin Med. 2000 Nov; 136(5):371-378). In this article, the authors state that: "Simple iron salts such as chloride, sulfate and ascorbate are considered too toxic for parenteral administration, because dissolution of these compounds liberates free iron." This statement and subsequent statements in the article regarding the toxic activity of free iron are supported in the article with eight references to journal articles published from 1950 to 1999. (Declaration, paragraph 5).

In view of the above, Applicant submits that: (1) a reference describing inclusion of iron dextran in a dialysate does not read on the presently-pending claims, which recite "an iron complex dissolved in the water, the complex ... having a molecular weight of less than about 50,000," and (2) a reference describing inclusion of iron dextran in a dialysate would not motivate a person of ordinary skill in the art to select a low molecular weight iron complex (referred to in the present specification as a "primary complex") for inclusion in a dialysate composition.

Turning now to Bellini et al., this reference does not teach or suggest, and would not motivate a skilled artisan to make or use, a dialysate composition including iron gluconate. In this

regard, it is again important to acknowledge the widespread and generally accepted belief that soluble iron, or free iron, induces a toxic reaction when contacted with blood in any form other than a tightly-bound, non-soluble macromolecule such as iron dextran. When reading the Bellini et al. reference against this background of information, it is clear that Bellini et al. did not contemplate, nor did they intend to suggest, that it would be desirable to deliver iron to a patient via peritoneal dialysis in the form of iron gluconate. (Declaration, paragraph 7). Indeed, such a suggestion is so contradictory to the generally held belief that such a suggestion would have been immediately discredited by a person of ordinary skill in the art as a simple error unless it were accompanied by a full description, including examples of test results, showing that such a composition is not toxic. (Declaration, paragraph 7). The absence of any such information in the Bellini et al. reference supports the conclusion that Bellini et al. did not contemplate, teach or suggest delivery of iron to a patient via dialysate or inclusion of iron gluconate in a dialysate composition. (Declaration, paragraph 7).

Indeed, the Bellini et al. reference is not directed to iron delivery technology at all, but is rather directed to providing alternative osmotic substances, other than glucose, for inclusion in peritoneal dialysates. In this regard, Bellini et al. discloses "solutions for peritoneal dialysis that contain an osmotic substance which is an alternative to glucose." (Col. 1, lines 1-3). More specifically, Bellini et al. disclose "a peritoneal dialysis solution ...characterized in that it comprises an osmotic substance chosen among gluconic acid and its pharmaceutically acceptable salts." (Col. 2, lines 30-34). Furthermore, the concentration of a gluconic acid and/or salt in a peritoneal dialysis solution is described in Bellini et al. in functional terms of providing a final osmolarity of between 200 and 500 mOsm/l. (Col. 2, lines 43-47).

The Bellini et al. reference includes a list of gluconic acid salts, including calcium gluconate, zinc gluconate, sodium gluconate, sodium stibogluconate, magnesium gluconate and iron gluconate (Col. 2, line 57 through Col. 3, line 1). However, this list would be considered by a person of ordinary skill in this art to be a generic list of sources of gluconic acid. (Declaration, paragraph 9). No example is provided in this reference of any experiment in which iron gluconate was included in a peritoneal dialysate, and a person of ordinary skill in the art would not have been motivated to select iron gluconate for such use in view of the widespread fear of iron toxicity. A person or ordinary skill in the art would have concluded that iron gluconate was simply included in this list in error, without consideration of the negative physiologic effect that it would have been believed to cause. (Declaration, paragraph 9). Therefore, Bellini et al. does not teach, suggest or enable a peritoneal dialysis protocol using a dialysate including iron gluconate, and it would not motivate a person of ordinary skill in the art to include iron gluconate in a dialysate.

In addition, Bellini et al. states that: "Advantageously, gluconic acid and/or any salts thereof are included in the peritoneal dialysis solution according to the present invention at a concentration of 1 to 5% by weight and therefore of 10 g/l up to 50 g/l." (Col. 2, lines 38-42). If iron gluconate were selected as the gluconic acid salt in Bellini et al., the dialysate would include from 10 g/l up to 50 g/l of iron gluconate, which would equal from about 91,000 to about 455,000 μg/dl of iron in the peritoneal dialysate. While this dialysate may have good osmotic properties by virtue of a gluconic acid salt, a person of ordinary skill in the art would dismiss any notion of including iron gluconate as the source of the gluconate salt, concluding that a peritoneal dialysate including iron gluconate, especially from about 91,000 to about 455,000 μg/dl of iron from iron gluconate, would be toxic. The lower end of this range is a concentration

of iron that is more than 300 times greater than the iron concentrations in dialysate concentrates described and claimed in the present application.

In the outstanding Action, the Examiner takes the position that a person of ordinary skill in the art would optimize the iron content for iron delivery as a matter of routine experimentation. In this regard, the Examiner asserts that:

> The ordinary skilled artisan in this field is a highly educated and trained medical professional responsible for critical care of dialysis patients, who would not blindly formulate dialysis solution ingredients to induce a toxic reaction...it would have been through routine experimentation that he/she would have arrived at the appropriate concentrations of electrolytes and iron gluconate or iron dextran (with a molecular weight of less than 50,000) suitable for a dialysis patient in need of iron supplementation as claimed.

The above statements, however, imply that a skilled artisan would first specifically contemplate delivering iron to a patient by including iron gluconate in a dialysate. Indeed, this is a necessary prerequisite to "arriving at the appropriate concentration for a dialysis patient in need of iron supplementation." Applicant submits, however, that a skilled artisan would not be motivated by Bellini et al. to deliver iron to a patient via dialysate in the first instance, and therefore this prerequisite is not met. Bellini et al. would not motivate a person of ordinary skill in the art to determine an "appropriate amount" or to include even a small amount of iron gluconate in a dialysate. Indeed, the skilled artisan would instinctively be motivated not to use iron gluconate in any amount due to the belief that the iron gluconate would have a detrimental impact on the patient's blood. (Declaration, paragraph 11). No suggestion or motivation exists in Bellini et al. or any other prior art of record to make or use a dialysate including an iron complex "having a concentration in the water to provide an iron concentration of from about 1 to about 250 μg/dl" or a dialysate concentrate including electrolytes and an iron complex with "concentrations in the water whereby the composition is effective for dilution to provide a dialysate having ... an iron

concentration of from about 1 to about 250 μg/dl" as recited in the pending claims. A skilled artisan would not "through routine experimentation...have arrived at the appropriate concentrations of...iron gluconate...suitable for a dialysis patient in need of iron supplementation" as asserted by the Examiner because a skilled artisan simply would not have contemplated delivering iron to a patient in this manner and would not have selected iron gluconate for inclusion in a dialysate in the first instance. (Declaration, paragraph 11). Absent identification of such a suggestion in the prior art, the invention recited in the present claims cannot be considered obvious under Section 103.

Applicant agrees with the Examiner's assertion that, "The ordinary skilled artisan in this field is a highly educated and trained medical professional responsible for critical care of dialysis patients, who would not blindly formulate dialysis solution ingredients to induce a toxic reaction." Indeed, for this very reason, an ordinary skilled artisan in this field prior to the present invention would not have incorporated an iron complex having a molecular weight of less than about 50,000 into a dialysate because this education and training would have included significant information regarding the widespread belief that such an ingredient would cause a toxic reaction. An ordinary skilled artisan would not blindly include an ingredient believed to induce a toxic reaction and therefore prior to the present invention, such an artisan would not have included in a dialysate composition an iron complex as recited in the pending claims.

Because a person of ordinary skill in the art would find no suggestion or motivation in cited references to practice the presently-claimed invention, Applicant respectfully submits that claims 24-29, 31-37, 39-41, 44 and 46-66 are allowable over the references of record and request that the rejection of these claims under 35 U.S.C. § 103(a) be withdrawn.

CLOSING

In view of the above, Applicant respectfully submits that the present application, as amended and including pending claims 24-29, 31-37, 39-41, 44 and 46-66, is in condition for allowance. Action to that end is respectfully requested. If there are any remaining issues that can be addressed telephonically, the Examiner is invited to contact the undersigned to discuss the same.

FOR THE RECORD

To touch briefly on a now-mooted point, Applicant regrets any miscommunication that may have occurred to result in the Examiner previously withdrawing the now-reinstated ground of rejection without fully understanding Applicant's position. The following remarks are provided in an effort to clarify the record.

Applicant respectfully disagrees that Applicant's earlier statement in Paper No. 13 was in error, and regrets that the Examiner feels that he was misled thereby. Applicant's prior statement to which the Examiner refers is the following:

> With respect to [the Examiner's citation of Applicant's specification as an admission that intraperitoneal delivery of iron dextran is known], Applicant notes again that the present application claims priority to a U.S. Provisional Application filed prior to the date of this reference; however, this information would not in any event provide any teaching or suggestion to a person of ordinary skill in the art to practice the presently claimed invention due to the widespread belief that soluble iron would be toxic if it were to be contacted with blood, discussed more fully below.

The subject statement in the specification of the regular application is the following: "Recently, it has been proposed that iron may be administered to a mammal by intraperitoneal delivery of macromolecular iron dextran."

To clarify Applicant's intended point in Paper No. 13, Applicant merely intended (1) to remind the Examiner that the present application claims priority to a prior-filed U.S. provisional

patent application, (2) to assert that the above-quoted statement in the specification of the subsequently-filed regular patent application is not an admission of prior art in view of the application's earlier effective filing date; and (3) to note that the status of the information as prior art is immaterial because "this information would not in any event provide any teaching or suggestion to a person of ordinary skill in the art to practice the presently claimed invention."

Applicant continues to believe that its assertion in Paper No. 13 is correct, and submits that no legal precedent or other support has been provided for the conclusion that the newly-cite prior art (Medline accession numbers 70113694 and 76201043) somehow converts the specification statement into prior art and makes Applicant's assertion erroneous. Applicant believes that the finality of the outstanding Action was improper in view of the newly-cited prior art. Nevertheless, this issue is now moot in view of the present Request for Continued Examination.

Respectfully submitted,

By _____

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